UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/579,222	01/09/2007	Guenter Hoelzemann	24945-0034.US	7107

7590 04/29/2008

Ronald J. Kamis
Baker & Daniels
805 15th Street, N.W.
Suite 700
Washington, DC 20005

EXAMINER	
JAISLE, CECILIA M	

ART UNIT	PAPER NUMBER
1624	

MAIL DATE	DELIVERY MODE
04/29/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/579,222	HOELZEMANN ET AL.	
	Examiner	Art Unit	
	CECILIA M. JAISLE	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 February 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-14,17,18,20-30 and 32-39* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1-11,38 and 39* is/are allowed.

6)☒ Claim(s) *12-14,17,18,20-30 and 32-37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *11-20-2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Withdrawal of Restriction

The Restriction Requirement set forth in the Office Action of Sep. 7, 2007 was in error, because this application was filed under 35 U.S.C. 371, and the restriction is accordingly withdrawn. Claims 1-14, 17, 18, 20-30 and 32-39, all of the claims in this application, are under examination.

Rejection Under 35 USC 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12-14, 17, 18, 20-30 and 32-37 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* inhibition of VEGF-stimulated mitogenesis of HUVECs (pages 43-57, *inter alia*), does not reasonably provide enablement for treatment of diseases comprising inhibiting, regulating or modulating any kinase signal transduction (claims 12, 28, 29, 30); diseases of all tyrosine kinases and all Raf kinases (claims 13, 32); where the tyrosine kinases are TIE-2, VEGFR, PDGFR, FGFR and FLT/KDR (claim 14); where the disease is cancer (claims 17, 34), where the cancer is tumors of squamous epithelium, bladder, stomach, kidneys, head, neck, esophagus, cervix, thyroid, intestine, liver, brain, prostate, urogenital tract, lymphatic system, stomach, larynx or lung (claims 18, 37);

where the cancer is lung adenocarcinoma, small-cell lung carcinoma, pancreatic cancer, glioblastoma, colon carcinoma or breast carcinoma (claim 20); where the cancer is of the blood or immune system (claim 21); where the disease of the blood or immune system originates from monocytic leukemia acute, myelotic leukemia, chronic myelotic leukemia, acute lymphatic leukemia or chronic lymphatic leukemia (claims 22, 37); where the disease implicates angiogenesis (claim 23); where the disease is an ocular disease (claim 24); where the ocular disease is retinal vascularisation, diabetic retinopathy, age-induced macular degeneration or an inflammatory disease (claim 25); where the inflammatory disease originates from rheumatoid arthritis, psoriasis, contact dermatitis or delayed hypersensitivity reaction (claim 26); where the disease is of bone pathologies originating from osteosarcoma, osteoarthritis or rickets (claim 27); where the disease is hyperproliferative or non-hyperproliferative disease (claim 33); where the disease is non-cancerous (claim 35); or where the non-cancerous disease is psoriasis, arthritis, inflammation, endometriosis, scarring, benign prostatic hyperplasia, immunological disease, autoimmune diseases or immuno-deficiency disease (claim 36). The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The following reasons apply to this enablement rejection.

The instant claims cover diseases known to exist and that may be discovered in the future, for which no enablement is provided. The claimed scope includes the recited specific diseases as well as undiscovered disorders associated with these diseases.

The specification discloses that the compounds of the present claims provide *in vitro* inhibition of VEGF-stimulated mitogenesis of HUVECs (pages 43-57, *inter alia*).

Many if not most diseases said to be controlled or protected against by the claimed compounds, such as cancer, etc., are known as difficult to treat. At present no known drug can successfully prevent or reverse the course of many of these diseases, despite the fact that many drugs are said to provide *in vitro* inhibition of VEGF-stimulated mitogenesis of HUVECs. Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Also, note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses.

Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 66 FR 1092-1099 (2001), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq*. This disclosure is not sufficient to enable the claimed methods based solely on the disclosed CDK4 inhibitory activity.

MPEP § 2164.01(a) states:

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. In re Wright, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the claim breadth; (2) the nature of the invention; (3) the state of the prior art; (4) the level of predictability in the art; (5) the amount of direction provided by the inventor; (6) the presence of working examples; and (7) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (Fed.Cir. 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

1. **Breadth of the claims:**

(a) Scope of the methods. The claims cover methods using substituted pyridopyrimidinones to treat all diseases by inhibiting, regulating or modulating kinase signal transduction, especially tyrosine kinases and Raf kinases.

A kinase (i.e., phosphotransferase) is an enzyme type that transfers phosphate groups from high-energy donor molecules, such as ATP, to specific target molecule substrates in a process termed phosphorylation. The largest group of kinases are protein kinases, which act on and modify the activity of specific proteins to transmit signals and control complex cellular processes. Up to 518 different kinases have been identified in humans. Various other kinases (named after their substrates) act

on small molecules (e.g., lipids, carbohydrates, amino acids, nucleotides, etc.), either for signaling or to prime them for biochemical reactions in metabolism.

A protein kinase is a kinase enzyme that modifies other proteins by chemically adding phosphate groups to them. This class of protein is further separated into subsets such as PKC alpha, PKC beta, and PKC gamma, each with specific functions. Phosphorylation can chang enzyme activity, cellular location, or association with other proteins. Up to 30% of all proteins may be modified by kinase activity, and kinases are known to regulate the majority of cellular pathways, especially those involved in signal transduction, the transmission of signals within the cell. The human genome contains about 500 protein kinase genes.

The chemical activity of a kinase involves removing a phosphate group from ATP and covalently attaching it to one of three amino acids that have a free hydroxyl group. Most kinases act on both serine and threonine, others act on tyrosine, and a number (dual specificity kinases) act on all three.

Because protein kinases have profound effects on a cell, their activity is highly regulated. Kinases are turned on or off by phosphorylation, by binding of activator proteins or inhibitor proteins, or small molecules, or by controlling their location in the cell relative to their substrates.

Tyrosine kinases are a subclass of protein kinase. A tyrosine kinase is an enzyme that can transfer a phosphate group from ATP to a tyrosine residue in a protein. Tyrosine kinases are a subgroup of the larger class of protein kinases.

Phosphorylation of proteins by kinases is an important mechanism in signal transduction for regulation of enzyme activity.

Broadly, kinases include such diverse groups as serine/threonine-specific protein kinases, including calcium/calmodulin-dependent protein kinase II (CaMKII), cAMP/cGMP, diacylglycerol, and Ca^{2+}/calmodulin, tyrosine-specific protein kinases, including Platelet-derived growth factor (PDGF) receptor, Epidermal growth factor (EGF) receptor, Insulin receptor and insulin-like growth factor (IGF1) receptor, and Stem cell factor (*scf*) receptor, receptor tyrosine kinases, receptor-associated tyrosine kinases, such as Janus kinase (JAK), histidine-specific protein kinases, aspartic acid/glutamic acid-specific protein kinases, and mixed kinases, including MEK (MAPKK), a mixed serine/threonine and tyrosine kinase.

PTK Group - `Conventional' protein-tyrosine kinases

1.PTK group I Src family

2.PTK Group II Tec/Atk family

3.PTK Group III Csk family

4.PTK Group IV Fes (Fps) family

5.PTK Group V Abl family

6.PTK Group VI Syk/ZAP70 family

7.PTK Group VII Tyk2/Jak1 family

8.PTK Group VIII Ack family

9.PTK Group IX Focal adhesion kinase (Fak) family

10.PTK Group X Epidermal growth factor receptor family

11.PTK Group XI Eph/Elk/Eck receptor family

12.PTK Group XII Axl family

13.PTK Group XIII Tie/Tek family

14.PTK Group XIV Platelet-derived growth factor receptor family

15.PTK Group XV Fibroblast growth factor receptor family

16.PTK Group XVI Insulin receptor family

17.PTK Group XVII LTK/ALK family

18.PTK Group XVIII Ros/Sevenless family

19.PTK Group XIX Trk/Ror family

20.PTK Group XX DDR/TKT family

21.PTK Group XXI Hepatocyte growth factor receptor family

22.PTK Group XXII Nematode Kin15/16 family

23.PTK Other membrane spanning kinases

Moreover, members of a group can be substantially different. For example, the pattern of expression of JAK3 contrasts sharply even with that of other Janus kinases (JAK1, JAK2, and TYK2), which are ubiquitously expressed, as opposed to JAK3 whose expression appears to be limited to certain cells. In addition, even a single kinase can exist in numerous variants.

(b) Scope of the diseases covered. The claims cover methods for treatment of all of the diseases mentioned above, including other diseases that may be discovered in the future that may be comprehended under the recited diseases.

Cancer includes breast and colon cancers, carcinomas of the prostate, lymphoma, leukemia and many others. Breast cancers come in great variety. The most important category of breast cancers is the ductal cancers, which come in a wide variety of types, divided into categories: intraductal (*in situ*); invasive with predominant intraductal component; invasive, NOS; comedo; inflammatory (IBC); medullary with lymphocytic infiltrate; mucinous (colloid) carcinoma; papillary carcinoma; scirrhous; tubular and others. Another category is lobular breast cancers: *in situ*, invasive with predominant *in situ* component and invasive. Paget's disease of the nipple can be also with intraductal carcinoma or with invasive ductal carcinoma. Adenomyoepithelioma is a dimorphic tumor characterized by the presence of both epithelial and myoepithelial cells. There is breast angiolipoma and spindle cell lipoma of the breast. There is lymphoma of the breast (which exists in both Non-Hodgkin's lymphoma of the breast and Hodgkin's disease of breast forms). There are some sarcomas, including giant cell sarcoma of the breast, leiomyosarcoma of the breast, Angiosarcoma of the breast, cystosarcoma phylloides and liposarcoma of the breast. There are carcinoid tumors that can be primary carcinoid tumors of the breast or can arise from nonmammary sources. There are breast salivary gland-like tumors, including acinic cell carcinoma (AcCC), oncocytic carcinoma (Mammary epithelial oncocytoma) and mucoepidermoid carcinoma (MEC). Other rare carcinomas include Spindle cell carcinoma of the breast (SpCC), Squamous cell carcinoma of the breast, Secretory Carcinoma of the Breast (Juvenile secretory carcinoma), Metaplastic carcinoma of the breast (a heterogeneous group

of invasive breast cancers including types with squamous differentiation and those with heterologous elements), Invasive Micropapillary Carcinoma of the Breast, Adenoid cystic carcinoma of the breast, cribriform carcinoma, Myofibroblastoma of the Breast (Benign spindle stromal tumor of the breast) and glycogen-rich clear cell carcinoma of the breast. There are numerous other rare breast cancers, including for example Fibromatosis of the breast (extra-abdominal desmoid), Angiomatosis of the Breast and mammary hamartoma. There are also nonmammary tumors, primarily adenocarcinomas, that can metastasize to the breast, including bronchogenic carcinomas, malignant melanomas (primary and secondary), rhabdomyosarcomas, malignant mesotheliomas, thyroid carcinomas, renal cell carcinomas, malignant lymphomas and gastrointestinal carcinomas (including those from the stomach, pancreas, esophagus and colon).

The category of colon cancers includes many types which are rather diverse. Most are adenocarcinomas, either of the mucinous (colloid) type or the signet ring type. Less common colon cancers include squamous cell, neuroendocrine carcinomas, carcinomas of the scirrhous type, lymphomas, melanomas (which can be primary or metastatic), sarcomas (including fibrosarcomas and Leiomyosarcomas) and Carcinoid tumors.

Carcinomas of the prostate are usually adenocarcinomas, but others include small cell carcinoma, mucinous carcinoma, prostatic ductal carcinoma, squamous cell carcinoma of the prostate, basal cell carcinoma, neuro-endocrine carcinoma, signet-ring cell carcinomas and others.

Leukemia includes four different types of blood cancers: Acute Myelogenous, Acute Lymphocytic, Chronic Myelogenous and Chronic Lymphocytic Leukemias. The ways individuals with leukemia are affected and treated, and the rate at which the disease progresses, are different for each type of leukemia. Lymphoma is a general term for a cancer group originating in the lymphatic system and divided into two major categories: Hodgkin lymphoma and non-Hodgkin lymphomas.

Autoimmune diseases include blood diseases, e.g., Aplastic Anemia, Autoimmune Hemolytic Anemias, joint diseases, e.g., Ankylosing Spondilitis, muscle diseases, e.g., Polymyositis/dermatomyositis, ear diseases, e.g., Autoimmune Hearing Loss and Meniere's Syndrome, eye diseases, e.g., Mooren's Ulcer, Reiter's Syndrome, Vogt-Koyanagi-Harada Disease, kidney diseases e.g., IgA Nephropathy, skin diseases e.g., Alopecia Areata, Bullous Pemphigoid, Epidermolysis Bullosa Acquisita, Pemphigus Foliaceous, Vitiligo, cardiovascular diseases, e.g., Autoimmune Myocarditis, Vasculitis, Churg-Strauss Syndrome, Giant Cells Arteritis, Kawasaki's Disease, Polyarteritis Nodosa, Takayasu's Arteritis, Wegener's Granulomatosis, endocrine diseases, e.g., Addison's Disease, Autoimmune Hypoparathyroidism, Autoimmune Hypophysitis, Autoimmune Oophoritis, Autoimmune Orchitis, Graves' Disease, Hashimoto's Thyroiditis, Polyglandular Autoimmune Syndromea Types 1, 2 and 3 and Type 1 Diabetes Mellitus, gastroenteric diseases, e.g., Autoimmune Hepatitis, Celiac Disease, Inflammatory Bowel Disease and Primary Biliary Cirrhosis, nervous diseases, e.g., Chronic Inflammatory Demyelinating Polyneuropathy, Guillan-Barre Syndrome, Multiple

Sclerosis, Myasthenia Gravis and systemic diseases, e.g., Antiphospholipid Syndrome, Autoimmune Lymphoproliferative, Autoimmune Polyendocrinopathy, Bechet's Disease, Goodpasture's Syndrome , Rheumatoid Arthritis, Sarcoidosis, Sjogren's Syndrome and Systemic Lupus Erythematosus. All neurodegenerative diseases are recognized as chronic.

Lupus is an autoimmune disease that affects various parts of the body, including the skin, joints, heart, lungs, blood, kidneys and brain. Inflammation is considered the primary feature of lupus, characterized by pain, heat, redness, swelling and loss of function, inside and/or outside the body. Lupus currently has no cure.

Psoriasis includes various forms, such as Plaque, Guttate, Inverse, Pustular, and Erythrodermic; defined by its location on the body, including Scalp psoriasis, Genital psoriasis, psoriasis On the face, On the hands and feet, and Psoriasis of the nails; and psoriatic arthritis includes Symmetric arthritis, Asymmetric arthritis, Distal interphalangeal predominant, Spondylitis and Arthritis mutilans.

Arthritis refers to any kind of inflammation of the joints arising from a wide diversity of causes and mediators, many of which are unknown. It mostly commonly refers to any of osteoarthritis, rheumatoid arthritis (RA), traumatic arthritis, rubella arthritis, neuropathic arthritis, infectious arthritis or gouty arthritis. These are totally different and unrelated disorders, which all have “arthritis” in their name and involve inflammation of the joints. RA is an inflammatory disorder causing destruction of articular cartilage, in which macrophages accumulate in the rheumatoid synovial membrane. Mediators are cytokines, including IL-1, IL-18, α-TNF and IFN. It is thus

an autoimmune condition where the body's immune system attacks its joints. In gouty arthritis, joint inflammation is caused by the formation of monosodium urate monohydrate (MSU) crystals within the joint space. Osteoarthritis is a degenerative cartilage disorder; cartilage breakdown causes bones to rub against each other. Causes include injuries, diseases such as Paget's disease, and long-term obesity, but often the cause is unknown, and the full mechanism has not been discovered. There is also Psoriatic Arthritis (including DIP and spondylitis) that is believed to be autoimmune in origin but is a separate disorder from RA.

Inflammatory diseases include Granulomatous inflammation, such as tuberculosis, leprosy and syphilis, Fibrinous inflammation, such as serous cavities, Purulent inflammation, such as staphylococci infection, Serous inflammation, Ulcerative inflammation, allergic reactions, myopathies, and many immune system disorders. Non-immune diseases with etiological origins in inflammatory processes include cancer, atherosclerosis and ischemic heart disease, other disorders associated with inflammation include, Asthma, Autoimmune diseases, Chronic inflammation, Glomerulonephritis, Hypersensitivities, Inflammatory bowel diseases, Pelvic inflammatory disease, Reperfusion injury, Rheumatoid arthritis, Transplant rejection and Vasculitis. Adult (or Acute) Respiratory Distress Syndrome (ARDS) is severe inflammation in both lungs resulting in an inability of the lungs to function properly. ARDS is a devastating, often fatal, inflammatory lung condition that usually occurs in conjunction with catastrophic medical conditions, such as pneumonia, shock, sepsis, and trauma. No specific therapies currently exist for ARDS patients.

Treatment primarily involves supportive care in an intensive care unit, including use of a mechanical ventilator and supplemental oxygen to help patients breathe.

The specification fails to identify the results of treatment with the methods of this invention and how such results would be recognized, particularly with regard to conditions and diseases that are currently considered fatal.

2. **Nature of the invention and predictability in the art:** The invention is directed toward medicine and is therefore physiological in nature. It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved," and physiological activity is generally considered to be an unpredictable factor. See *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970).

Pharmacological activity in general is unpredictable. In applications involving physiological activity, such as the present:

> The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.

Plant Genetic Systems v. DeKalb Genetics Corp., 65 USPQ2d 1452 (CAFC 2003).

3. **Direction and Guidance:** That provided is very limited. The dosage range information is meager at best. It is generic, the same for all disorders the specification covers. No specific direction or guidance provides a regimen or dosage effective specifically for all of the conditions construed by the claims.

4. **State of the prior art:** The art indicates the need for undue experimentation.

Arora, et al., J. Pharmacol. & Experim. Therap., Vol. 315, No. 3, 2005, pp. 971-979, conservatively reports:

> At the present time, tyrosine kinase inhibitors serve more as second- or third-line therapies rather than as primary therapy. They may also be useful in combination with traditional cytotoxic chemotherapy. For the tyrosine kinase inhibitors to have a primary role in therapy, there has to be a clear hypothesis for their use, relevant preclinical data, and a demonstrated use in well characterized groups of patients. So far, these criteria have not been met for most of the presently available tyrosine kinase inhibitors.

Hynes, Breast Cancer Res., 2000, 2, pp. 154-157, hypothesizes, only in regard to breast cancer, "Finally, considering the concept of cooperativity between proteins that induce breast cancer, it is likely that therapeutic combinations directed at multiple molecular targets may prove to be more efficacious than monospecific therapy in the treatment of breast cancer."

Batchelor, et al., Cancer Cell, 11, 83-95, Jan. 2007, reports limited, disease-specific results of tumor vasculature normalization and edema alleviation in glioblastoma patients with AZD2171, a Pan-VEGF receptor tyrosine kinase inhibitor.

> [W]e report an immediate and significant normalizing effect of AZD2171 in 16 patients with recurrent glioblastoma – indicative of a direct effect on tumor vasculature – with promising tumor responses and biomarker correlations. … Since AZD2171 monotherapy may not increase survival, future trials of AZD2171 with or without chemotherapy are planned to validate these findings and test these hypotheses.

There is no indication in this specification that the present compounds function as Pan-VEGF Receptor tyrosine kinase inhibitors.

Fu, et al., J. Nat. Cancer Inst., Vol. 95, No. 12, Jun. 18, 2003, suggests:

> In summary, our results suggest that RKIP [Raf kinase inhibitor protein] functions as a suppressor of metastasis. Furthermore, our data demonstrate that decreased RKIP expression is associated with increased invasive ability, vascular invasion, and angiogenesis. This is the first study, to our knowledge, to document the association between a cancer progression-associated decreased expression of a molecule that inhibits

signal transduction and increased metastasis. These results suggest that inhibition of the MEK-ERK pathway may prevent metastasis.

Thus, ability of an agent that inhibits tyrosine and Raf kinases activity to treat all the diseases recited by the claims remains open to further study and proof.

5. **Working Examples:** Applicants do not provide highly predictive competent evidence or recognized tests to treat all conditions recited for the claims. Furthermore, Applicants have not provided competent evidence that the instantly disclosed tests are highly predictive for all uses disclosed and embraced by the claim language for all of the intended hosts.
6. **Skill of those in the art:** Arora, Hynes, Batchelor, and Fu call into question the efficacy of treatment with the claimed methods. These references discussed above confirm the need for additional research.
7. **Quantity of experimentation needed to make or use the invention.** Based on the disclosure's content, an undue burden would be placed on one skilled in the pharmaceutical arts to use the invention, since the disclosure gives the skilled artisan inadequate guidance regarding pharmaceutical use, for reasons explained above. The state of the art, as discussed in the articles referenced above, indicates the requirement for undue experimentation, particularly with regard to potentially devastating side effects. Thus, the ability of an agent that inhibits tyrosine and Raf kinases activity to treat all of the diseases construed by the present claims remains open to further study and proof.

See MPEP 2164.01(a), discussed *supra*, justifying the conclusion of lack of enablement commensurate with the claims. Undue experimentation will be required to practice Applicants' invention.

Allowed Claims

Claims 1-11, 38 and 39 are allowed. Following is an examiner's statement of reasons for allowance: WO/2002/44156, published Jun. 6, 2002 (cited by Applicants) describes benzimidazole derivatives with aromatic ureido moieties, useful as TIE-2 and/or VEGFR2 inhibitors, but fails to describe the specific combination of heterocycles and substituents of the presently claimed compounds or their methods of preparation.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to CECILIA M. JAISLE, J.D. whose telephone number is (571)272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/James O. Wilson/
Supervisory Patent Examiner, Art Unit 1624

CECILIA M. JAISLE, J.D.
4/21/2008